

REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Status of Claims

1. Claims 1-34 and 39-76 are currently pending in the present application.
2. Claims 69-76 have been withdrawn from consideration by the Examiner for reasons stated in the Restriction Requirement mailed June 29, 2005.
3. Applicants reserve the right to pursue the subject matter of any withdrawn or cancelled claims in one or more continuing applications.
4. Following the above amendments claims 1-34 and 39-76 remain pending in the present application.

II. Claim Rejections Under 35 U.S.C. § 103(a)

5. Claims 1-34 and 39-76 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Cunningham et al., US Patent No. 5,849,535, in view of Jespersen et al., and further in view of Houk et al. Applicants respectfully traverse this rejection.
6. It is submitted that this rejection is moot as it was previously applied in the Office Action mailed November 29, 2005, based on the same prior art references and on the same statutory ground. The withdrawal of this former rejection was acknowledged by the Examiner as set forth on page 2, first paragraph, of the present Office Action.
7. Further, it is respectfully submitted that a *prima facie* obviousness rejection has not been established by the combination of the teachings of Cunningham et al. and

Jespersen et al. and Houk et al. The Examiner has noted that Cunningham et al. does not use mercapto compounds as reducing agents to decrease the trisulfide impurity. The additional teachings of Jespersen et al. and Houk et al. taken in combination with Cunningham et al. fail to provide the additional teachings to make obvious to one of skill in the art the use of a mercapto compound to decrease the amount of a trisulfide isoform impurity produced in a recombinant production process for a growth hormone antagonist polypeptide.

8. The Examiner cites Jespersen et al. for teaching the characterization of a trisulphide derivative of human growth hormone produced in *E. coli*. While Applicants agree that Jespersen et al. does characterize the trisulfide derivative of human growth hormone, Applicants' disagree that this reference serves as a proper basis to make obvious, in combination with Cunningham et al. and Houk et al., Applicants' invention. Applicants submit that 1-4-dithiothreitol and cysteine were only used by Jepersen et al. to characterize the novel protein derivative, see Abstract at page 365. The Jespersen et al. paper does not teach a method as presently claimed for reducing the amounts of impurities in the recombinant production of growth hormone or even suggest that the reagents used to characterize the protein derivative should be included in a recombinant manufacturing process to decrease the amount of this impurity.

9. The Examiner cites Houk et al. for discussing the structure – reactivity relations for a number of thiol compounds, which are functional equivalents of compounds recited in the application. Applicants disagree. The paper of Houk et al. classifies cyclic disulfides into three groups based on reduction potential and based on stability toward ring-opening polymerization, see conclusion, page 6832, column 2. While there is the notation of the use of thiol-disulfide interchange reaction in biochemistry, there is simply no teaching or suggestion to use the teaching of Houk et al. in combination with Cunningham et al. and Jespersen et al. for reducing a trisulfide isoform of human growth hormone in a recombinant suspension of human growth hormone.

10. In view of the above remarks, Applicants request the withdrawal of the obviousness rejection and reconsideration of claims 1-34 and 39-68.

III. Conclusion

12. Applicants submit that all the grounds for rejection of the pending claims have now been overcome and that all the claims are now in condition for allowance, which action is respectfully requested.

13. In the event that the Examiner wishes to discuss this case he is requested to contact the undersigned attorney.

Respectfully submitted,



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Date: September 21, 2007

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